REMARKS

This Amendment amends claim 16 to recite the pharmaceutically acceptable agent is an acid having a dissociation constant in the range of from 6.7 to 7.4. Page 6, lines 3-5 of the specification supports this amendment. Claims 16, 19-22 and 28-30 are pending.

A Request for Continued Examination (RCE) is attached. Accordingly, entry of this Amendment is requested.

The 35 U.S.C. § 103(a) rejection of claims 16, 19-22 and 28-30 over U.S. Patent No. 5,494,676 to Stab et al. in view of PCT Patent Publication WO 02/07520 to Wei et al. is traversed. The claimed method includes administration of a pharmaceutical composition comprising a pharmaceutically acceptable agent or salt thereof capable of acidifying cell cytoplasm, wherein the pharmaceutically acceptable agent is an acid having a dissociation constant in the range 6.7 to 7.4, and wherein the agent is mixed with a carrier to adjust the pH of the composition to a range of 6.1 to 7.0. The claimed method specifies an effective amount of the pharmaceutically acceptable agent be administered in non-dissociated form to a person or animal.

As an initial matter, "non-dissociated form" means the pharmaceutically acceptable acid is mainly in its non-dissociated

form, which is achieved by adjusting the pH of the composition to a pH of 6.1 to 7.0, as recited in claim 16.

Contrary to the statements in the Official Action, not all pharmaceutically acceptable agents are capable of acidifying cell cytoplasm. In fact, there are many agents which exist in both dissociated and non-dissociated form at a pH of 6.1 to 7.0 (i.e. they have a pKa value at the approximate range of 6 to 7), but which are incapable of acidifying cell cytoplasm. Examples of such agents (including polyprotic acids) are adenosine-5'-triphosphate (ATP; pKa 6.5), which, in addition to being the main energy source to cells, has also important cell signalling functions, recognized and bound by cell surface purinergic receptors; histamine (pKa 6.0), which is a well known biogenic amine mediating many cellular functions in the brain and immune system by binding to cell surface histamine receptors; and ergometrine (pKa 6.8), which is an alkaloid with LSD-like complex pharmacology with multiple receptor binding properties and which is sometimes used to prevent bleeding after childbirth. None of these agents act by acidifying cell cytoplasm, or is capable of acidifying cell cytoplasm.

In order to be able to acidify cell cytoplasm, an agent must fulfill several criteria. First and most importantly, the agent

should accumulate in the cell cytosol, i.e., it should be able to move from the extracellular space into the cell interior and locate itself in the cytoplasm. To the applicants' knowledge, none of the agents mentioned as examples above are known to accumulate in the cell cytoplasm from the extracellular space. Secondly, the agent should not interfere with other systems in the cell physiology, i.e., it should not be taken up or consumed by other biochemical events, such as receptor binding, enzyme activity, etc., which would prevent its accumulation in the cytoplasm. In short, the determination of whether a given agent is capable of acidifying cell cytoplasm requires experimental work. One of ordinary skill in the art would be not able to apprehend this property simply by knowing the agent's pKa.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed method because one of ordinary skill in the art would not combine the references as suggested by the Patent office. Stab et al. fails to disclose or suggest mixing its pharmaceutically acceptable agent (cis-urocanic acid) with a carrier to adjust the pH of the composition to a range of 6.1 to 7.0. Instead, the pH of Stab et al.'s cream is

4.74. See the Declaration Pursuant to 37 C.F.R. 1.132 by Dr. Jarmo Laihia, of record.

Wei et al. is cited to show motivation to use topical compositions at a "relatively neutral pH". However, one of ordinary skill in the art would not consider Wei et al. when seeking a method to treat a local, inflammatory disease or disorder. Wei et al. teaches a two-component composition for use as antimicrobial in the treatment of mastitis, which comprises a) a chlorine dioxide generating component, which in turn comprises an acid-forming compound and a metal chlorite, and b) an antimicrobial fatty acid. The acid-forming component and the metal chlorite react in a chemical reaction to produce chlorine dioxide, a gaseous, oxidizing agent used for disinfection. The fatty acid is used to maintain the antimicrobial activity over a longer period (page 4, lines 13-14). The pH of the composition is about 5 to about 10, most preferably about 5.5 to about 8 (page 4, lines 9-18).

Wei et al. is not relevant to the claimed method for the following reasons:

1. Wei et al. discloses an *antimicrobial* composition, useful to kill microbes, but which would not be useful for controlling the

hyperactivity of leukocytes seen in inflammations. Inflammation may be caused by a microbial infection but also by many other reasons, such as tissue trauma, hypersensitivity reaction (i.e. allergy), or autoimmune reaction.

2. The pH range taught by Wei et al. (about 5 to about 10) is significantly broader than the crucial pH region (6.1-7.0) used in the claimed method, particularly when it is remembered that pH is a logarithmic scale. Wei et al. does not teach or suggest its composition should be adjusted to a pH range of 6.1 to 7.0.

3. Wei et al. is completely silent about intracellular acidification.

4. Wei et al.'s two-component composition is intended to kill micro-organisms; not to enter and acidify the cytoplasm of the host's cells such as neutrophils or other leukocytes to cause an anti-inflammatory effect based on acidification of such cells.

5. None of the components in Wei et al. has a dissociation constant in the range 6.7 to 7.4; instead, claim 3 requires the pKa of the acid-forming components to be less than about 4.5.

Even assuming, arguendo, Wei et al. is analogous prior art, one of ordinary skill in the art would *ignore* Wei et al.'s suggestion that a relatively neutral pH will minimize skin

irritation because it has no solid scientific basis. See, e.g. Murahata et al., 18 J. Am. Acad. Dermatol. 62-66 (1988); and Antoine et al., 37 Derm. Beruf. Umwelt. 96-100 (1989) (copies enclosed), which found no correlation between skin irritation and the pH of an applied agent at a pH range 4 to 10.5.

In short, one of ordinary skill in the art would have no motivation to adjust Stab et al. cis-UCA composition to a pH range 6.1 to 7.0 to minimize skin irritation. Reconsideration and withdrawal of the obviousness rejection of claims 16, 19-22 and 28-30 over Stab et al. in view of Wei et al. are requested.

The 35 U.S.C. § 103(a) rejection of claims 16, 19-22 and 28-30 over Ben-Bassat et al., 6 Current Pharm. Design 933-942 (2000) in view of PCT Patent Publication WO 02/07520 to Wei et al. is also traversed. As discussed above, the claimed method includes administration of a pharmaceutical composition comprising a pharmaceutically acceptable agent or salt thereof capable of acidifying cell cytoplasm, wherein the pharmaceutically acceptable agent is an acid having a dissociation constant in the range 6.7 to 7.4, and wherein the agent is mixed with a carrier to adjust the pH of the composition to a pH range of 6.1 to 7.0. The claimed method specifies an effective amount of the pharmaceutically acceptable

agent be administered in non-dissociated form to a person or animal.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed method. The Patent Office concedes Ben-Basset et al. fails to expressly disclose adjusting the pH of tyrosine kinase inhibitors such as compound AG 18 to a range of 6.1 to 7.0.

The Patent Office makes an unsupported argument that the pKa of compound AG 18 is 7.24. However, the pKa of compound AG 18 is about 8.24 - this is a theoretical estimate based on structural calculations. See http://ibmlc2.chem.uga.edu/sparc/. Assuming this pKa value, compound AG 18 would be completely dissociated in a composition having a pH of 6.1 to 7.0, and thus be unable to acidify cell cytoplasm. Indeed, compound AG 18 would act as a base, increasing the pH of the cytoplasm.

One of ordinary skill in the art would not combine Wei et al. with Ben-Bassat et al. for the reasons discussed above in the previous rejection. Moreover, he would ignore Wei et al.'s suggestion to use a "relatively neutral pH" in view of Murahata et al. and Antoine et al., which found no correlation between irritation and the pH of the applied agent at a pH of 4 to 10.5.

Reconsideration and withdrawal of the obviousness rejection of claims 16, 19-22 and 28-30 over Ben-Bassat et al. in view of Wei et al. are requested.

The obvious-type double patenting rejection of claims 16, 19-22 and 28-30 over claims 16-21 and 23-26 of Application S.N. 10/565,202 in view of Granstein, 98 J. Clin. Invest. 1695-1696 (1996) is traversed. The '202 application has been abandoned. Reconsideration and withdrawal of the obvious-type double patenting rejection of claims 16, 19-22 and 28-30 over claims 16-21 and 23-26 of the '202 application in view of Granstein are requested.

The provisional obvious-type double patenting rejection of claims 16, 19-22 and 28-30 over claims 13-18 and 20-23 of copending Application S.N. 11/408,056 in view of Granstein is traversed. The allegedly conflicting claims have not yet been allowed. Since this application is otherwise in condition for allowance, the provisional rejection should be withdrawn. A corresponding non-provisional rejection can then be made in the '056 application, if appropriate. Reconsideration and withdrawal of the provisional, obvious-type double patenting rejection of claims 16, 19-22 and 28-30 over claims 13-18 and 20-23 of the '056 application in view of Granstein are requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of all rejections of claims 16, 19-22 and 28-30, and issuance of a Notice of Allowance directed to those claims, are earnestly requested. The Examiner is urged to telephone the undersigned should he believe any further action is required for allowance.

Fees for the RCE and the Petition for Extension of Time are being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

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Enclosures:
Petition for Extension of Time
Request for Continued Examination
Murahata et al., 18 J. Am. Acad. Dermatol. 62-66 (1988); and
Antoine et al., 37 Derm. Beruf. Umwelt. 96-100 (1989)